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Clinical Aspects of Hodgkin's Disease

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THOMAS HODGKIN, when demonstrator of pathology in Guy's Hospital, presented in 1832 to the London Medical and Chirurgical Society a paper entitled "Morbid Appearances of the Absorbent Glands and Spleen," in which he described a series of cases characterized by an enlargement of the lymphatic glands and of the spleen. The glands were of "a firm cartilaginous structure." The spleen was "thickly sprinkled with tubercles presenting the same structure as the glands." Hodgkin regarded these changes as a primary affection of glands and spleen, not secondary to inflammatory or tuberculous changes, and due to hypertrophy of pre-existing structures. This paper attracted little attention, and seems to have been forgotten till 1856. At this date Samuel Wilks published in Guy's Hospital reports a paper dealing with lardaceous disease. He included an account of a peculiar enlargement of the lymphatic glands, which he considered was an original observation, but discovered while the article was in the press that he had been forestalled by Dr. Hodgkin, and loyally acknowledged the senior man's priority.

Nine years later Wilks contributed an article on "Cases of Enlargement of the Lymphatic Glands and Spleen" to the same journal, in which he analyzed the six cases which had constituted Hodgkin's series, two of which he discarded as being discordant with the others. He then proceeded to describe twelve additional cases which he had himself collected. Wilks in this paper put Hodgkin among the immortals by attaching his name to the disease. When Wilks's series of cases is studied, it is evident that he included two cases of leukæmia, a condition which was the following year definitely distinguished from Hodgkin's disease by Wunderlich. Wilks recognized that this disease formed a link between the granulomata, such as tuberculosis, and malignant disease.

In the course of its history, no other disease has been burdened with so many synonyms. It has been known as lymphosarcoma (Virchow), pseudo-leukæmia (Cohnheim), adénie (Trousseau), lymphadenoma (Wunderlich), lymphogranulo-

matosis, etc. These names are but an index of the obscurity which has so long enveloped its etiology. Probably "Hodgkin's disease" is the most non-committal name to employ when referring to this syndrome, some of whose atypical forms may yet prove to be distinct and separate diseases.

The disease is one of young adult life, the onset of the disease being rare after forty years of age. The commonest period of onset is between twenty and thirty, but many cases occur in the first, second, and fourth decades. I have seen the condition in a woman of seventy-five. Males are affected more than twice as frequently as females. Many writers stress the possibility of preceding sepsis as a predisposing factor. The cervical glands are the group most commonly affected. The area drained by these glands — mouth, teeth, tonsils, naso-pharynx, nasal cavity, and its sinuses, is the favourite seat of focal infection. In the exceptional cases where other groups are primarily involved, a previous history of sepsis nearby is not uncommon. I had under my care a young woman who after her confinement developed a sepsis of the breast while nursing her infant. The axillary glands of the corresponding side became enlarged. These were the precursors of a generalized lymphadenoma. Lord Horder relates the case of the only patient he had seen in which the first glands to be enlarged were the inguinal. In this case the disease followed a urethritis and bubo of the groin. He also narrates the rapidly fatal case of a surgeon in which the disease arose in the glands of the armpit. This followed three months after the healing of a septic finger of the hand on the same side.

The usual course of the disease is that described by Trousseau :—

1. Stage of local lymph-node enlargement.
2. Stage of generalized lymph-node enlargement.
3. Stage of cachexia.

Stage of Local Enlargement of Lymph-nodes.—The patient seeks medical advice on account of a swelling on one or other side of the neck. Except for the anxiety, inconvenience, or disfigurement produced by the mass of enlarged glands, there is no complaint of pain nor of any change in the general health. On palpation one finds a bunch of glands, not unlike a bunch of grapes, with the larger glands in the centre, and the smaller ones towards the periphery. There is no evidence of caseation or inflammatory changes; the overlying skin is not adherent nor reddened. The absence of inflammatory and infiltrative changes explains the characteristics of the individual glands, which are painless and insensitive, smooth, discrete, and easily movable. The disease appears to have as a site of election the glands of the posterior triangle, especially those in the supra-clavicular and post-auricular regions, although any of the other groups may be involved. The glands may reach a quite enormous size, scarcely paralleled by any other type of glandular enlargement.

Stage of Generalized Enlargement of Lymph-nodes.—After a variable period, other groups of glands make their appearance, signalling the onset of the stage of generalized enlargement of the lymphatic nodes. The advance as a rule takes place in an orderly manner, the disease spreading from one neighbouring group to the next. The glands on the other side of the neck become involved; the axillary glands

become palpable, especially the subclavicular and subpectoral group, and even the epitrochlear gland may be palpable. Although it is true that the inguinal glands may be the next to become evident, it is illogical to believe that the disease can jump from axilla to groin. Rather we must postulate, although direct evidence is often lacking, that the course is rather through mediastinal and bronchial groups to the retroperitoneal and hence by the mesenteric and iliac to the inguinal. And in this lies the hidden menace of this disease.

The early diagnosis of enlargement of the internal glands is fraught with almost insuperable difficulties, but the further course of the disease and post-mortem experience warn us that their involvement must be suspected. Later I shall stress the importance of recognizing that the deep glands may be the initial site of the disease. It is expedient to realize that when the axillary or inguinal glands are palpable, by this time also the mediastinal and tracheo-bronchial and abdominal groups are also involved. Sooner or later evidence of their presence is shown by physical signs or pressure symptoms. Abnormal areas of dullness in the chest should be carefully sought for. As the anterior mediastinal glands are favourite intrathoracic sites, dullness to right, left, and under the sternum in its upper part may be found. Careful attention should be paid to pressure symptoms—as intra-thoracic pain, cough (often paroxysmal), dyspnœa, hoarseness due to interference with the recurrent laryngeals, evidence of bronchial obstruction and pleural effusions, cyanosis of the face, turgidity of the jugular veins, alterations in the size of the pupils, difficulty in swallowing, and clubbing of the fingers. Careful X-ray of the chest should be carried out.

In over half the cases the spleen is sufficiently enlarged to be palpable, but its enlargement rarely reaches the dimension found in the leukæmias or in splenic anæmia. The edge of the liver in a smaller proportion of cases can be felt below the right costal margin. It is rare to be able to palpate the glands in the abdomen, but in one case observed, the retroperitoneal glands were huge enough to produce a mass which filled the larger part of the abdomen.

The swelling of the abdominal glands produces various symptoms; of these in my experience, severe and persistent pain simulating sciatica, due to pressure on the lumbar and sacral plexus, is common. Pressure on the coeliac plexus may give rise to a pigmentation not unlike that seen in Addison's disease. Pressure exerted by the glands in the hilum of the liver may lead to jaundice and ascites; while pressure on the large venous trunks may lead to œdema of the lower extremities.

Remembering the large amount of lymphoid tissue in the alimentary tract, it is surprising that this area should so often escape. It is but rarely that the tonsils are attacked, and symptoms pointing to involvement of Peyer's patches and of the appendix are rather of pathological interest than of clinical importance.

Although the absence of infiltration is a striking feature in lymphadenoma, yet it may and does occur, often with disastrous results. Fisher has already reported from my wards two cases of this nature. A large intrathoracic mass eroded and invaded the body of the fourth dorsal vertebra, producing collapse of the body. This woman suffered agonies of pain from pressure on the posterior nerve-roots, and

ultimately developed paraplegia. A second case developed paraplegia without X-ray evidence of infiltration of the vertebral column. It is possible that the tumour mass made its way through an intervertebral foramen and so caused a pressure paraplegia. It is interesting to notice that in this case the cerebro-spinal fluid was peculiar. Only about 5 c.c. of colourless fluid were obtained. Pressure on the jugular veins did not increase the rate of flow. The fluid was highly albuminous, approximately .2 per cent., and contained fifty cells per c.m., thus differing from the ordinary Froin's syndrome in the fact that the cells were increased.

Various constitutional symptoms manifest themselves during this period. The temperature, which is normal during the stage of local enlargement, becomes irregularly intermittent. A peculiar type of relapsing fever is of special importance. This was first observed by Murchison in Hodgkin's disease, but was later more fully studied by Pel and Ebstein, and known as the Pel-Ebstein syndrome. A period of pyrexia of ten to fifteen days' duration occurs, the temperature gradually rising in staircase fashion to a maximum, and then steadily falling by lysis. This is followed by an apyrexial period of another ten or fourteen days, when the temperature again rises. This cycle may occur over many months.

Sweating and pruritus are often very troublesome features of the disease. They may be early symptoms. An engineer aged 35 developed marked itchiness, chiefly in his groins and armpits. This itch persisted for two years, and was followed by sweating at night. At this time he did not notice any of his glands swollen. Probably, however, some of the internal glands were already involved. He came to hospital on account of night sweats and of general weakness. Glands were discovered in his groin; one of these was removed and found to show the typical histological appearances of Hodgkin's disease. There is some evidence to show that sweating and pruritus are associated with exacerbations of gland activity, and we have noted that during these periods an eosinophilia may appear in the blood.

Stage of Cachexia.—As the disease advances, cachexia sets in and the patient becomes rapidly more anæmic. There is no typical blood-picture in Hodgkin's disease, and a diagnosis cannot be made from the blood alone. The anæmia shows a greater fall in the hæmoglobin than in the red corpuscles—there is usually a low colour index. The number of leucocytes vary from a leucocytosis of moderate degree to a leucopenia. The variation in the number of the eosinophils is of importance. In two cases lately we have found the percentage nineteen and ten during a period of pruritus; at other times in the same patient these cells were within normal limits. The platelets are said to be increased.

Wasting may be marked in the cachetic stage, one of my patients losing over two stones in weight—from 8 st. 6 lb. to 6 st. 5 lb.—in a few months before her death.

Prognosis.—The prognosis in this disease is uniformly fatal. Probably two to three years is a fair expectation of life from development of symptoms, though many cases run a much more rapid course. In those cases in which the mediastinal or retroperitoneal glands are markedly involved, the outlook is especially grave.

Cases in which the superficial glands are chiefly affected may live five or more years. At any time a patient whose downward progress has been slow may show a sudden exacerbation of gland enlargement and the disease takes on a quickly downward course. Death in Hodgkin's disease is usually due to anæmia and exhaustion, or from direct pressure effects on vital structures.

DIAGNOSIS.—In a straightforward case seen in the stage of generalized enlargement of the glands with a palpable spleen, the diagnosis is not difficult. The diseases with which it is likely to be confused are lymphatic leukæmia and infectious mononucleosis or glandular fever, but the examination of the blood gives the required clue. Lympho-sarcomatosis may exactly simulate Hodgkin's disease, but the more constant presence of a mediastinal tumour, with greater infiltrative powers, its lesser tendency to pyrexia, and the fact that the spleen is much less frequently enlarged, may be suggested as points in the differential diagnosis; but, on the other hand, mediastinal tumour is not uncommon in Hodgkin's, and it may infiltrate neighbouring structures, as has already been described; Hodgkin's too may be afebrile, and quite frequently the spleen is not palpable. Hence the exact diagnosis must always be from the histological or biological examination of an excised gland.

In the early stage of Hodgkin's, when we are confronted with a localized swelling of the glands in the neck, the differential diagnosis is again difficult. Careful search should eliminate the question of local sepsis. Malignancy as a cause of localized enlargement may cause difficulty. I can recall a case of enlarged supraclavicular glands, where the primary focus was a bronchial carcinoma which until late in the disease gave rise to no clinical symptoms, although a persistent cough was suggestive. Here the diagnosis was established by excision of a gland before any definite clinical evidence of the primary growth was forthcoming. The tendency of the affected glands to form early adhesions, their peculiar hardness and the presence of radiating pain, suggest malignancy. From tuberculosis of the cervical lymph-glands the diagnosis is simple, if the tuberculous glands are tender and adherent, if they have softened, or if the overlying skin is inflamed, or if an actual sinus or old scar is present, or if tuberculosis be found elsewhere in the body. Tuberculous glands have not the same pronounced hardness nor are they so prominent as those of Hodgkin's disease. Quervain aptly remarks that the whole aspect of Hodgkin's disease resembles a caricature of tuberculous adenitis. But occasionally the diagnosis is far from evident, and the various classical clinical symptoms fail. The rare condition of generalized tuberculous adenitis is especially difficult. I have recently had in my ward a young woman who had enlarged glands in both sides of her neck, in axillæ, and inguinal regions. For many years she had been diagnosed as Hodgkin's disease. However, finally some of the glands caseated and broke down. X-ray examination showed a remarkable degree of calcification in cervical, intrathoracic, and abdominal glands—those in the neck forming almost a collar of chalk around the neck. Calcification is practically unknown in Hodgkin's disease. Excision of a gland in this case showed typical tuberculous changes. Later she developed caries of the second cervical vertebra. The exact diagnosis of a

tuberculous gland infection is of vital importance for the patient, the prognosis and treatment being so different in the two cases. The tuberculin reaction may assist, but the most satisfactory method is biopsy. It is important to remember that occasionally the enlarged glands of Hodgkin's may become secondarily infected by tuberculosis, but Gordon has shown that the incidence of tuberculosis is scarcely greater in the glands taken from cases of lymphadenoma than in a series of control glands.

A still greater difficulty arises in those cases where the disease plays its "signature tune" in an unexpected manner. For instance, I have already cited a case where pruritus and sweating were initial symptoms and their true etiology remained long unguessed. I have seen a case in which pain in the chest, due to pressure of a huge mass of enlarged mediastinal glands, caused the patient to seek advice, and at that time only a few unobstrusive glands in the left supraclavicular region could be found and which had entirely escaped the patient's observation. The disease starting with enlargement of the axillary glands, of the inguinal glands, or of the spleen, may all be very puzzling, unless this possibility is borne in mind. But probably the most difficult type for diagnosis, fortunately rare, is that in which no evidence of superficial glandular enlargement can be found and the spleen is not enlarged, the so-called "latent" or "larval" type. The following case illustrates the difficulty in diagnosis in this type of case. For fourteen months a man had at intervals pyrexial attacks which were accompanied by ordinary febrile symptoms. These attacks were separated by an interval of fourteen days' freedom from fever. In the early stages of his illness he carried on his work in an insurance office during the febrile period. As the condition continued he was forced to go to bed during the attack, but returned to work during the afebrile period. Finally, as weakness, anæmia, and wasting became gradually more marked, he discontinued work completely. He was frequently examined by many physicians; his blood again and again gave negative agglutination results to the enteric group and to bacillus abortus, his leucocytes were not increased; blood cultures, urinary examinations, X-ray examinations of chest and abdomen, and cholecystography threw no positive light on the case. He was admitted apparently *in extremis* to the Royal Victoria Hosiptal, emaciated and slightly jaundiced, with a greatly distended and protuberant abdomen, temperature 103, pulse 130. To our great surprise he began to improve, jaundice disappeared, and as the temperature fell he recovered to a surprising degree. However, after eleven days' freedom from temperature, his temperature again rose, jaundice reappeared, the liver became palpable, and he died just as his temperature was subsiding after fourteen days of a typical Pel-Ebstein pyrexia. While in hospital various examinations were repeated, with negative results. Unfortunately an autopsy was absolutely refused, but I have little doubt that the diagnosis suggested by the peculiar type of temperature and by a process of exclusion of other conditions, namely a larval type of lymphadenoma, was the correct one.

TREATMENT.—Two methods of treatment are in the present state of our therapeutic knowledge of value—deep X-ray or radium therapy, and the use of arsenic.

There is a general consensus of opinion that irradiation has prolonged the period of remission, especially in the early stages of Hodgkin's disease, and has reduced pressure symptoms, and so rendered the remaining span of life not only longer but more endurable.

I have repeatedly seen a localized focus of lymphadenoma tissue completely disappear under X-ray treatment and pressure symptoms relieved. But in spite of local success, recurrences sooner or later occur in the same area or in other regions, and with each recurrence the interval of remission becomes shorter and the fresh glands more resistent to irradiation. The failure to maintain the early success in the later stages is most disappointing. However, the difficulties of the radiologist seem to me almost insuperable. The wide dissemination of the disease throughout the thoracic and abdominal cavities militates against a dosage adequate to cause regression of all the affected nodes. The greatest success has been in cases where the disease is caught in its early localized condition in the neck. Unfortunately, this stage is too rarely diagnosed; most of our cases have advanced well into the generalized stage before treatment has been instituted. Enlarged glands in any part of the body demand urgent and exact diagnosis, and their successful early recognition is of special importance in Hodgkin's disease, if the unfortunate patient's only hope is not to be sacrificed. Between the intervals of X-ray treatment, arsenic should be pushed, either in the form of Fowler's solution, sodium cacodylate, or nov-arseno-billon.

To the knowledge of this disease first described by Hodgkin while working as a morbid anatomist, clinicians have added but little. It has gradually been isolated from a scrapheap of allied conditions, chiefly by the advance of pathological technique. To the pathologists we turn hopefully for further light on its causation, with a lively faith that the elucidation of this strange intermediate disease may be the stepping-stone to the solution of the infinitely more pressing problem of malignancy.

Hodgkin's Disease: Pathological Aspects

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PATHOGENESIS.

THE natural jumping-off place for any consideration of the pathology of lymphadenoma should be a concise account of its pathogenesis. Unfortunately this is still unknown. At one time or another many different organisms have been incriminated —the tubercle bacillus, human, bovine, and avian; diphtheroid bacilli, spirochætes, and various fungi—but now there is an increasing probability that none of them has anything to do with the etiology of the disease. A thorough re-investigation of